

Heart Failure

Long-Term Clinical Effect of Hemodynamically Optimized Cardiac Resynchronization Therapy in Patients With Heart Failure and Ventricular Conduction Delay

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OBJECTIVES	We sought to compare the short- and long-term clinical effects of atrial synchronous pre-excitation of one (univentricular) or both ventricles (biventricular), that provide cardiac resynchronization therapy (CRT).
BACKGROUND	In patients with heart failure (HF) who have a ventricular conduction delay, CRT improves systolic hemodynamic function. The clinical benefit of CRT is still being investigated.
METHODS	Forty-one patients were randomized to four weeks of first treatment with biventricular or univentricular stimulation, followed by four weeks without treatment, and then four weeks of a second treatment with the opposite stimulation. The best CRT stimulation was continued for nine months. Cardiac resynchronization therapy was optimized by hemodynamic testing at implantation. The primary end points were exercise capacity measures. Data were analyzed by two-way repeated-measures analysis of variance.
RESULTS	The left ventricle was selected for univentricular pacing in 36 patients. The clinical effects of univentricular and biventricular CRT were not significantly different. The results of each method were pooled to assess sequential treatment effects. Oxygen uptake during bicycle exercise increased from 9.48 to 10.4 ml/kg/min at the anaerobic threshold ($p = 0.03$) and from 12.5 to 14.3 ml/kg/min at peak exercise ($p < 0.001$) with the first treatment, and from 10.0 to 10.7 ml/kg/min at the anaerobic threshold ($p = 0.2$) and from 13.4 to 15.2 ml/kg/min at peak exercise ($p = 0.002$) with the second treatment. The 6-min walk distance increased from 342 m at baseline to 386 m after the first treatment ($p < 0.001$) and to 416 m after the second treatment ($p = 0.03$). All improvements persisted after 12 months of therapy.
CONCLUSIONS	Cardiac resynchronization therapy produces a long-term improvement in the clinical symptoms of patients with HF who have a ventricular conduction delay. The differences between optimized biventricular and univentricular therapy appear to be small for short-term treatment. (J Am Coll Cardiol 2002;39:2026–33) © 2002 by the American College of Cardiology Foundation

Both natural (1,2) and experimentally induced (3) ventricular conduction delays generate uncoordinated ventricular contractions that reduce the pumping effectiveness of the heart (4), and they have been linked with a poor outcome in heart failure (HF) (5–7). Electrophysiologic and hemodynamic studies of patients with HF who have a predominantly left ventricular (LV) conduction delay have shown significant improvements in LV systolic function (8,9), with decreased myocardial energy demand (10), when simultaneously pre-exciting the right ventricle (RV) and LV

(biventricular) or just the LV synchronized to sinus rhythm. This biventricular or LV pre-excitation apparently resynchronizes RV and LV contractions (11), as well as LV septal and lateral wall contractions (12,13). Also, for patients with a prolonged atrioventricular (AV) delay, atrial synchronous pre-excitation improves AV timing (14,15). Collectively, we refer to these methods as cardiac resynchronization therapy (CRT).

Only the short-term effects of CRT, using nonoptimized biventricular stimulation, have been tested in clinical studies up to now (16–18). No randomized study has investigated whether the hemodynamic benefit, that is similar with biventricular and LV CRT (9), translates into a similar clinical outcome. The multicenter, patient-blinded, sequential-treatment, randomized, crossover Pacing Therapies for Congestive Heart Failure (PATH-CHF) pilot study was designed in 1995 to test the hypothesis that hemodynamically optimized CRT would produce a long-term improvement in the exercise tolerance and quality of

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Abbreviations and Acronyms

ANOVA	= analysis of variance
AV	= atrioventricular
CRT	= cardiac resynchronization therapy
ECG	= electrocardiogram/electrocardiographic
HF	= heart failure
LV	= left ventricle/left ventricular
NYHA	= New York Heart Association
PATH-CHF	= Pacing Therapies in Congestive Heart Failure study
RV	= right ventricle or ventricular
SDANN	= standard deviation of averaged normal R-to-R intervals

life of patients with severe HF, sinus rhythm and a ventricular conduction delay, who were receiving optimal, maximally tolerated pharmacologic therapy. The crossover of CRT methods was used to verify the hypothesis that LV-only stimulation, or RV-only stimulation, whichever is hemodynamically superior, would not have clinical effects significantly different from those of biventricular stimulation, when the stimulation is individually optimized to provide maximal initial hemodynamic improvement.

METHODS

Patients. Patients were eligible if they had New York Heart Association (NYHA) functional class III or IV symptoms for six months before enrollment, despite optimal pharmacologic therapy, which may have included an angiotensin-converting enzyme inhibitor, loop diuretic, vasodilator, nitrate, digitalis and beta-blocker, if tolerated. All patients had been diagnosed by coronary angiography as having dilated cardiomyopathy of any etiology, sinus rhythm ≥ 55 beats/min, a QRS complex duration ≥ 120 ms in at least two surface electrocardiographic (ECG) leads and a PR interval ≥ 150 ms.

Exclusion criteria have been previously described (17). Briefly, patients were excluded if they had primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to LV systolic HF), an indication for conventional pacemaker or implantable cardioverter-defibrillator or other noncardiac conditions that could limit their exercise capacity and life expectancy. The seven participating institutions' review boards approved the protocol, and all patients provided written, informed consent.

Protocol. After the initial evaluation, the patients were implanted with two dual-chamber pacemakers (Vigor or Discovery, Guidant Corp., St. Paul, Minnesota)—one endocardially connected to the right atrium and RV at the apex, and the other independently and endocardially connected to the right atrium and epicardially to the LV through a limited thoracotomy. At implantation, the patients were instrumented for acute hemodynamic testing, as previously reported in a preliminary analysis of the first 27

patients (9). The goals of hemodynamic testing were to select the optimal univentricular stimulation and to determine the best AV delay. The maximum rate of change in LV pressure and aortic pulse pressure were used for optimization (9). Pacemakers were programmed according to results of hemodynamic testing, as previously reported (19). An atrial synchronous tracking mode without atrial pacing (VDD mode) was programmed with a lower rate limit of 40 beats/min. The randomization was designed to achieve a 1:1 ratio for univentricular and biventricular stimulation (Fig. 1). At implantation, the patients who were blinded to the treatment sequence were randomized to four weeks of univentricular or biventricular stimulation (first treatment period), followed by four weeks of no treatment, and then the therapy was started again with the opposite stimulation for another four weeks (second treatment period). Clinical measurements were made at pre-implantation (baseline) and at the end of each period, or in case of early termination, before the patient entered the next period.

At the end of the second treatment period, patients continued to receive CRT. The attending physician selected long-term therapy programming that provided the best therapeutic effect, based on their judgment. Patients returned for clinical follow-up and cardiopulmonary testing at 12 months after implantation.

Clinical measurements. The primary end points were oxygen uptake at peak exercise, oxygen uptake at the anaerobic threshold and the 6-min walk distance. The secondary end points were changes in NYHA functional class and quality of life. All clinical data pertinent to the primary and secondary end points were independently reviewed for protocol compliance, uniformity of measurement procedures and final data analysis at the core centers, whose investigators were blinded to the patients' treatment. The 6-min walk distance and quality-of-life tests were administered by study nurses who had no knowledge of the patients' treatment. Cardiopulmonary exercise testing was conducted on an upright bicycle ergometer with a 10-W/min step protocol, starting with 2 min of unloaded cycling. The ventilatory threshold was measured by the V-slope method (20). The 6-min walk test was performed according to Bittner (21). The cardiopulmonary and walk tests were performed on different days. The self-administered Minnesota Living with Heart Failure questionnaire (22) was used for scoring quality of life on a scale from 0 (best) to 105 (worst). The mean and minimal heart rates and standard deviation of averaged normal R-to-R intervals (SDANN), which is a measure of heart rate variability (23), were obtained from custom-designed, digital 24-h ECG Holter monitors worn by 15 randomly determined patients at the end of each crossover period.

Statistics. The sample size was calculated at 53 patients, based on primary end point changes and variability for 80% power at a significance level of 0.05, as reported in the PATH-CHF study design (19). Because of the emerging availability of transvenous lead delivery systems, the Data

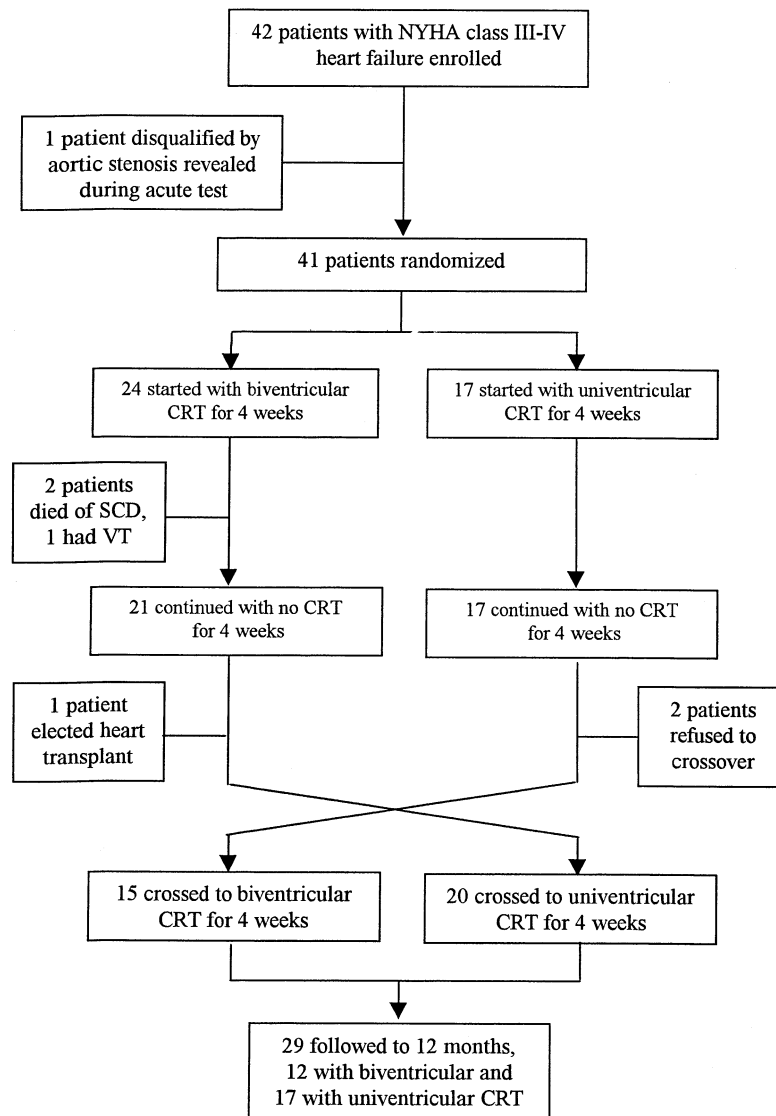


Figure 1. Flow chart of the Pacing Therapies in Congestive Heart Failure study, which was conducted between August 1995 and October 1998. CRT = cardiac resynchronization therapy; NYHA = New York Heart Association; SCD = sudden cardiac death; VT = ventricular tachycardia.

and Safety Monitoring Committee requested an independent statistician to re-assess the sample size, based on data from the first 27 patients. The Investigator Steering Committee decided to accept a new sample size of 42 to limit the number of thoracotomies, with the understanding that it might create an imbalance in the study groups.

The analysis of variance (ANOVA) model for acute hemodynamic testing has been extensively described (9). Two-way ANOVA with an additional co-variate to identify the effects due to stimulation order was used to compare univentricular and biventricular stimulation methods for continuous clinical variables, and the Wilcoxon matched-pairs test was used to compare methods for NYHA functional classes. Contingent on the nonsignificance of the stimulation method differences, repeated-measures ANOVA with the Tukey-Kramer multiple comparisons correction was used to evaluate period effects among the

baseline, first treatment, no treatment and second treatment periods for continuous clinical variables, and the Wilcoxon matched-pairs test was used to evaluate period effects for the NYHA functional classes. Crossover data were analyzed with the carry-forward principle for missing data. The 12-month data were analyzed by the paired *t* test and compared with the pre-implantation measurements. Data in the text are presented as sample mean value \pm SD.

RESULTS

Study group. Forty-two patients were enrolled in the study, and 41 patients received implants (Fig. 1). Their baseline characteristics are listed in Table 1. Most patients (71%) had a QRS duration >150 ms. All patients were in stable chronic HF under maximally tolerated pharmacologic therapy at implantation, including diuretics and anticoagu-

Table 1. Baseline Characteristics of the PATH-CHF Study Group

Characteristic	Randomized to Biventricular Stimulation (n = 24)	Randomized to Univentricular Stimulation (n = 17)	All Enrolled Patients* (n = 42)
Age (yrs)	59 ± 7	60 ± 5	60 ± 7
Gender (men/women)	11/13	10/7	21/21
Cause of heart failure			
Coronary artery disease	10 (42%)	1 (6%)	12 (29%)
Nonischemic dilated cardiomyopathy	14 (58%)	16 (94%)	30 (71%)
New York Heart Association Functional class (III/IV)	21/3	14/3	36/6
Electrocardiographic measurements			
Rest heart rate (beats/min)	77 ± 16	80 ± 13	78 ± 15
PR interval (ms)	190 ± 34	207 ± 30	196 ± 33
QRS duration (ms)	174 ± 30	178 ± 34	175 ± 32
Left bundle branch block	21 (87%)	17 (100%)	39 (93%)
Right bundle branch block	3 (13%)	0	3 (7%)
Echocardiographic measurements†			
LVEF (%)	21 ± 6	20 ± 7	21 ± 7
LVEDD (mm)	71 ± 10	75 ± 13	73 ± 11
LVESD (mm)	62 ± 9	68 ± 14	64 ± 12
Medication			
ACE inhibitor (captopril) or Digitalis (digoxin)‡	23 (96%)	17 (100%)	40 (95%)
Vasodilators or nitrates	17 (71%)	12 (71%)	29 (69%)
Beta-blockers (metoprolol)§	17 (71%)	11 (65%)	28 (67%)
Amiodarone	7 (29%)	6 (35%)	13 (30%)

*One enrolled patient was not randomized. †Patient with aortic stenosis excluded. ‡Dosage 98 ± 50 mg/day. §Dosage 40 ± 20 mg/day. ||Dosage 246 ± 88 mg/day. Data are presented as the mean value ± SD or number (%) of patients.

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

lants in all patients (Table 1). Implanted patients in each randomization group had similar baseline characteristics.

Implantation. The thoracotomy was well tolerated by all but one patient, who experienced sustained wound pain during preliminary treatment. Implantation of a LV lead was successful in all 41 patients in whom it was attempted. The LV lead was located on the apical to mid-lateral wall in two-thirds of the patients and on the anterior wall in one-third of the patients. In three patients, exit block developed due to increased stimulation thresholds. Treatable atrial fibrillation occurred in four patients, generally 48 to 72 h after implantation, and they required direct current cardioversion followed, in some cases, by anti-arrhythmic medication.

Initial hemodynamic response to ventricular stimulation. The hemodynamic data collected in all 40 patients in whom hemodynamic recording was possible, did not differ from the data previously reported for 27 patients (9). Atrial synchronous ventricular stimulation increased LV systolic function, but the magnitude of the increase depended on the site stimulated and the AV delay (Fig. 2). The systolic and diastolic responses to optimized univentricular and biventricular stimulation are compared in Table 2. These optimized responses were clinically very similar, within 2% for systolic measures and within 3% for diastolic measures. Based on these hemodynamic test results, the optimal

univentricular stimulation was selected to be the LV in 36 patients and the RV in 4 patients.

Comparison of univentricular and biventricular stimulation. The difference between the numbers of patients in the univentricular and biventricular groups was the result of early study termination (see Methods). The effect of the stimulation order during the crossover period was not significant for any clinical measure ($p > 0.504$). As shown in Table 3, which pools the treatment periods for each type of stimulation, there were no significant differences between the univentricular and biventricular stimulation effects on any end point. During the crossover period, there were no systematic changes in the drug regimen or dosage, except that the use of diuretics was reduced.

Sequential treatment effects. Measurements with both types of stimulation were pooled to analyze the effects of CRT compared with no treatment. The first and second treatment effects combined for all patients are shown in Table 4. After a four-week first treatment period administered immediately after implantation, all end points significantly improved from baseline. In contrast, at the end of the following no treatment period, the patients' NYHA functional class worsened compared with the first treatment period, and the bicycle exercise capacity declined to near baseline levels, whereas the 6-min walk distance and quality-of-life score improvements were unchanged. After

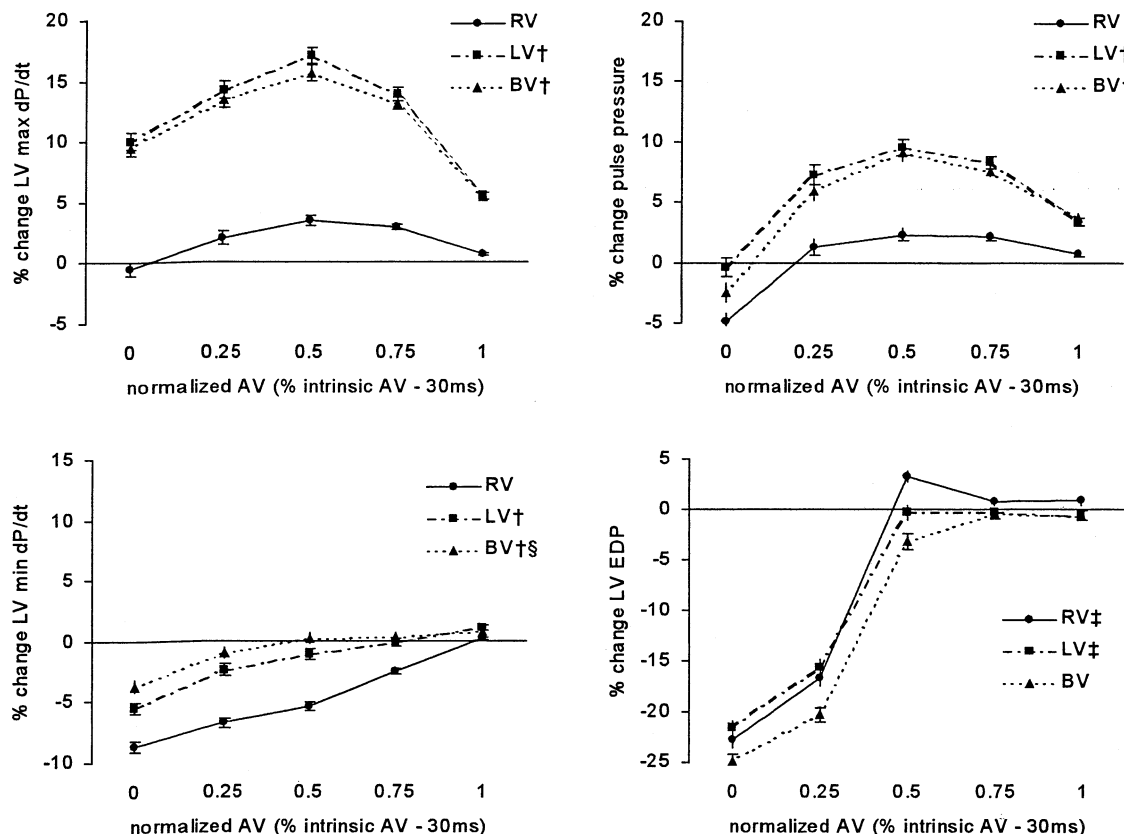


Figure 2. Comparison of hemodynamic responses to stimulation at different sites and atrioventricular (AV) delays, shown as the mean (\pm SEM) percent changes from baseline in the 40 patients in whom hemodynamic recording was possible. The **top plots** represent changes in systolic function and **bottom plots** represent changes in diastolic function. BV = biventricular stimulation; LV = left univentricular stimulation; LVEDP = left ventricular end-diastolic pressure; max dP/dt = maximum rate of change in left ventricular pressure; min dP/dt = minimum rate of change in left ventricular pressure; RV = right univentricular stimulation. **Legend symbols** indicate statistical differences between stimulation sites over all AV delays ($p < 0.001$). †LV > RV and BV > RV; ‡LV > BV and RV > BV; §BV > LV.

the second treatment period, both oxygen uptake at peak exercise and the 6-min walk distance significantly increased compared with the no treatment period (Table 4). Oxygen uptake at the anaerobic threshold and quality-of-life scores increased, but the effects were not significant. The patients' NYHA functional class was significantly improved, with 63% of the patients improving to class I or II in the second treatment period.

Table 2. Comparison of Initial Hemodynamic Responses to Optimized Univentricular and Biventricular Stimulation (Percentage Change from Baseline)

Parameter	Univentricular Stimulation*	Biventricular Stimulation	p Value†
Best AV delay (ms)	112 \pm 36	112 \pm 33	1
LVEP (%)	4.3 \pm 5.9	4.3 \pm 6.0	0.684
LVEDP (%)	-0.67 \pm 14.5	-3.7 \pm 16.0	<0.001
Aortic pulse pressure (%)	11.2 \pm 17.9	10.5 \pm 17.9	0.324
dP/dt _{max} (%)	18.4 \pm 16.6	17.0 \pm 15.8	<0.001
dP/dt _{min} (%)	1.3 \pm 8.6	1.8 \pm 9.6	0.258

*Left ventricular stimulation in 36 patients and right ventricular stimulation in 4 patients. †All p values were derived from paired comparisons with the Tukey-Kramer multiple comparisons correction following analysis of variance. Data are presented as the mean value \pm SD.

AV = atrioventricular; dP/dt_{max} = maximum rate of change in left ventricular pressure; dP/dt_{min} = minimum rate of change in left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVEP = left ventricular end-systolic pressure.

Heart rate changes. Compared with the no treatment period, the second treatment resulted in significant decreases in the mean heart rate (from 76.9 \pm 11.9 beats/min to 73.4 \pm 11.8 beats/min, $p = 0.01$) and minimal heart rate (from 62.7 \pm 13.5 beats/min to 57.4 \pm 12.6 beats/min, $p =$

Table 3. Biventricular Versus Univentricular Stimulation Clinical Effects

Clinical Measure	Biventricular Treatment	Univentricular Treatment*	p Value†
Oxygen uptake at peak exercise (ml/kg/min)	14.91 \pm 0.66	14.58 \pm 0.77	0.324
Oxygen uptake at anaerobic threshold (ml/kg/min)	10.70 \pm 0.47	10.39 \pm 0.51	0.290
6-min walk distance (m)	402 \pm 16	401 \pm 16	0.345
Quality-of-life score	25.2 \pm 3.3	28.1 \pm 3.5	0.069
NYHA functional class			0.360
IV	2 (5%)	3 (7%)	
III	17 (41%)	14 (34%)	
II	16 (39%)	15 (37%)	
I	6 (15%)	9 (22%)	

*Left ventricular stimulation in 36 patients and right ventricular stimulation in 4 patients. †All p values were derived from the F test for treatment method effects following analysis of variance, except for NYHA functional class, which was derived from the Wilcoxon matched-pairs test. Data are presented as the mean value \pm SEM or number (%) of subjects.

NYHA = New York Heart Association.

Table 4. Treatment Period Clinical Effects

Clinical Measure	Before Implantation	First Treatment	p Value*	No Treatment	Second Treatment	p Value*
Oxygen uptake at peak exercise (ml/kg/min)	12.50 ± 0.56	14.34 ± 0.63	<0.001	13.37 ± 0.67	15.15 ± 0.80	0.002
Oxygen uptake at anaerobic threshold (ml/kg/min)	9.48 ± 0.41	10.42 ± 0.43	0.026	10.00 ± 0.45	10.67 ± 0.55	0.198
6-min walk distance (m)	342 ± 17	386 ± 17	<0.001	394 ± 17	416 ± 15	0.028
Quality-of-life score	48.8 ± 3.4	29.5 ± 3.4	<0.001	29.8 ± 3.6	23.8 ± 3.2	0.062
NYHA functional class			<0.001			<0.001
IV	6 (15%)	3 (7%)		5 (12%)	2 (5%)	
III	35 (85%)	18 (44%)		22 (54%)	13 (32%)	
II	0	14 (34%)		11 (27%)	17 (41%)	
I	0	6 (15%)		3 (7%)	9 (22%)	

*All p values were derived from paired comparisons with the Tukey-Kramer multiple comparisons correction following analysis of variance, except for NYHA functional class, which was derived from the Wilcoxon matched-pairs test. Data are presented as the mean value ± SEM or number (%) of subjects.

NYHA = New York Heart Association.

0.003), which were associated with significant increases in heart rate variability (SDANN from 90.2 ± 28.6 ms to 117 ± 35.0 ms, $p < 0.001$).

Safety. Seven patients did not complete the crossover study (Fig. 1). The Data and Safety Monitoring Committee excluded one patient whose documented aortic stenosis was revealed at hemodynamic testing to be unacceptable for implantation. During the first treatment period, two patients died suddenly and one developed ventricular tachycardia. During the no treatment period, two patients refused to have the device switched off and voluntarily withdrew. Despite marked improvement in functional capacity, one patient elected for heart transplantation because of organ availability. In addition, one patient developed marked bradycardia requiring continuous atrial pacing at the end of the second treatment period.

One-year follow-up. At the end of the crossover phase, the attending physicians chose not to reprogram the CRT in 29 patients; they reprogrammed it from biventricular to univentricular stimulation in 2 patients and from univentricular to biventricular stimulation in 4 patients. At the end of 12 months after implantation, 29 patients (12 with biventricular, 13 with LV and 4 with RV) returned for follow-up testing. The magnitude of improvement at 12 months was similar to that observed at 3 months after implantation (Table 5). In the one year prior to implanta-

tion, 22 patients (76%) were hospitalized for HF with an average stay of 18.5 ± 16.7 days, whereas in the one year following implantation, 9 patients (31%) were hospitalized for HF with an average stay of 4.5 ± 9.3 days ($p < 0.001$, paired t test).

DISCUSSION

This is the first randomized study to show that different resynchronization methods provide similar short- and long-term clinical improvement when each method is individually optimized to provide maximal initial hemodynamic benefit in patients with severe HF associated with a ventricular conduction delay.

Cardiac resynchronization therapy improves exercise capacity and quality of life. Resynchronization therapy improved the patients' exercise capacity, NYHA functional class and quality of life after one month of treatment, as compared with baseline, and the improvements were repeatable after a second treatment period following one month when therapy was suspended. After one year, on average, the maximal exercise capacity had increased from 12.6 to 15.6 ml/kg/min, and 6-min walk performance increased from 357 to 466 m. Differences of this magnitude might improve the HF prognosis (24,25). Furthermore, complaints scored by the quality-of-life questionnaire were cut

Table 5. Clinical Changes After 12 Months of Long-Term Treatment

Clinical Measure	n	Before Implantation (Baseline)	12 Months of Treatment	p Value*
Oxygen uptake at peak exercise (ml/kg/min)	22	12.57 ± 0.63	15.63 ± 0.86	<0.001
Oxygen uptake at anaerobic threshold (ml/kg/min)	21	9.93 ± 0.46	11.45 ± 0.59	0.037
6-min walk distance (m)	25	357 ± 20	446 ± 15	<0.001
Quality-of-life score	28	48.6 ± 4.3	20.0 ± 4.1	<0.001
NYHA functional class	29			<0.001
IV		4 (14%)	0	
III		25 (86%)	8 (28%)	
II		0	11 (38%)	
I		0	10 (34%)	

*All p values were derived from the paired t test, except for NYHA functional class, which was derived from the Wilcoxon matched-pairs test. Data are presented as the mean value ± SEM or number (%) of subjects.

NYHA = New York Heart Association.

in half, and two-thirds of the patients improved to NYHA functional class I or II. Because patients were already on maximally tolerated, optimal pharmacologic therapy, including angiotensin-converting enzyme inhibitors and beta-blockers, these improvements represent a significant additional clinical benefit due to CRT.

Short- and long-term effects of CRT. Some of the clinical improvement in the first treatment period may be partially attributed to placebo effects. However, it is unlikely that the significant incremental improvements in the second treatment period can be attributed to a placebo effect, because clinical measures decreased to baseline levels or did not improve in the preceding patient-blinded, no treatment period. Notably, increases in peak oxygen uptake were as large with the second treatment as they were with the first treatment. It is also noteworthy that a persistent reduction in sympathetic tone occurred, as suggested by our evidence that the mean and minimal 24-h heart rates decreased, while heart rate variability increased, between the no treatment and second treatment periods. The rapidity with which CRT creates persistent changes is further suggested by the finding that clinical improvements were sustained but did not substantially increase from 3 to 12 months of continuous CRT.

Univentricular and biventricular CRT provide similar hemodynamic and clinical outcomes. Consistent with our hypothesis, the clinical differences between hemodynamically optimized biventricular and univentricular (predominantly LV) resynchronization methods were not significant, although our ability to differentiate was limited by a small sample size. Individual patients may benefit more with one than with the other resynchronization method, and differences between methods may become evident by longer follow-up. However, if this short-term similarity persists with long-term follow-up, a CRT system with only LV stimulation might be clinically useful. One possible interpretation of the similarity between the biventricular and LV treatments is that clinical improvement with CRT might depend on the magnitude of hemodynamic improvement due to CRT, which was similar for the optimized biventricular and LV methods.

Study limitations. Cardiac resynchronization therapy appears promising in terms of improving a patient's clinical symptoms, although the impact on mortality is unknown. Two patients had a sudden cardiac death, and one developed sustained ventricular tachycardia during the crossover period, consistent with the expected incidence of spontaneous ventricular tachyarrhythmias in this population (26). Also, two patients refused to continue the protocol in the four-week no treatment period, because they could not tolerate withdrawal of resynchronization therapy. Dropouts could have biased the results, because of the sequential crossover design. However, there were no significant differences between dropouts and other patients with respect to any parameter at baseline. Furthermore, we used the conservative carry-forward method for the missing data, which

tends to reduce the actual differences between treatment periods.

Hemodynamic and clinical improvements were demonstrated only in patients in NYHA functional class III or IV, with normal sinus rhythm and with a ventricular conduction disorder, primarily left bundle branch block. Results with other HF groups may differ. Cardiac resynchronization therapy remains technically challenging, and implantable devices expose patients to clinical risks, including device-related symptoms, device failure and surgical complications. Rapid technologic advances in device and lead design and implantation techniques are simplifying the implantation procedure and minimizing the risks (27).

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APPENDIX

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